Role of Immunotherapy of BTC

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Clinical trials, 1L, BTC

	Phase	Control	Experimental	OS (m)	HR
ABC-02	III	Gem	GemCis	8.1 vs 11.7	0.64
BT22	II	Gem	GemCis	7.7 vs 11.2	0.69
JCOG1113	III	GemCis	Gem+S1	13.4 vs 15.1	0.95 (non-inferiority)
KHBO1401-MITSUBA	III	GemCis	GemCis+S1	12.6 vs 13.5	0.79 (0.60-1.04)
Lee et al	III	GemOx	GemOx+Erlotinib	9.5 vs 9.5	0.93
BINGO	II	GemOx	GemOx+Cetuximab	12.4 vs 11.0	
Hezel et al	II	GemOx	GemOx+Panitumumab	10.2 vs 9.9	
JSBF	II	GemCis	GemCis+ Ramucirumab GemCis+Merestinib	13.0 vs 10.5 13.0 vs 14.0	1.33 (0.96-1.86) 0.95 (0.67-1.34)
NuTide	III	GemCis	NUC1031+Cis	negative	

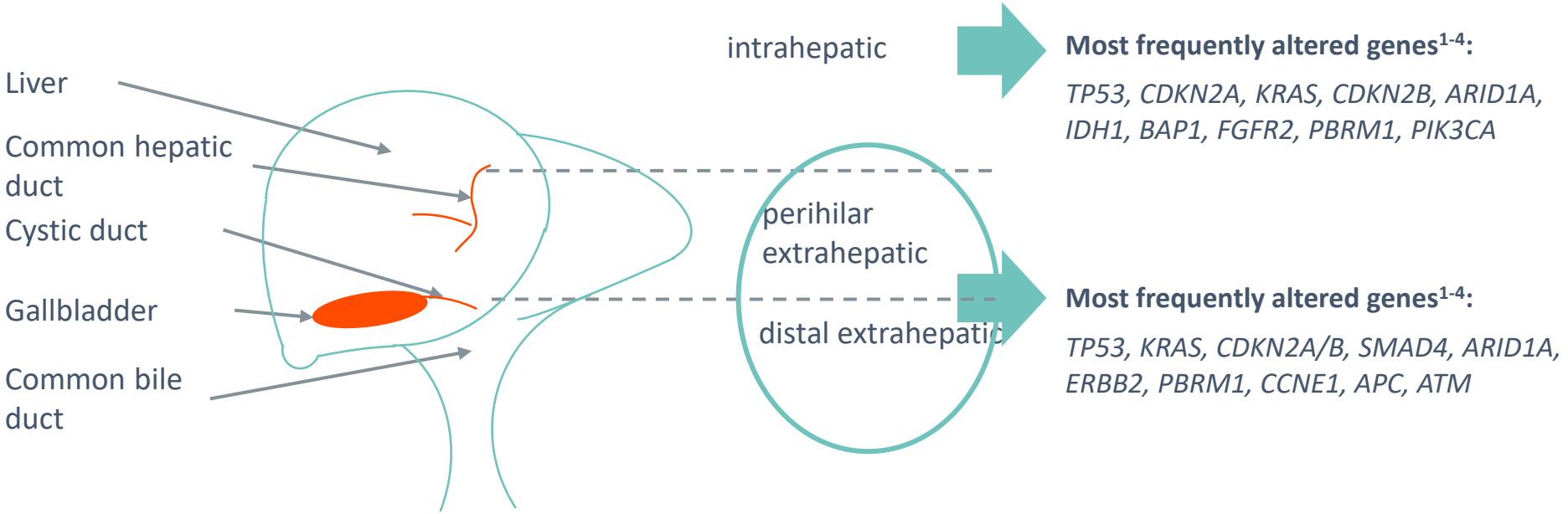
Each location has a different genomic profile and signature alterations

Genes associated with a good prognosis[1,2]:

FGFR2

Genes associated with a poor prognosis[1,2]:

EGFR, MET, BAP1, PBRM1, KRAS, TP53, MAPK/mTOR pathway, ARID2, CDKN2A/B, ERBB2 amplification*, ALK, ARID1A, PIK3CA, STK11, TGFBR2*



Given emerging evidence regarding actionable targets for treating cholangiocarcinoma, molecular testing of unresectable and metastatic tumours should be considered[2,3]

1. Lee, H., and Ross, J.S. (2017*) Ther Adv Gastroenterol* 10:507-20; 2. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancer (Version 4.2020) Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (Accessed June 2020); 3. Valle, J.W. et al. (2016) *Annals of Oncology* 27: V28-37; 4. Similie, M.M., et al (2019) *Medicina* 55: doi: 10.3390/medicina55020042.

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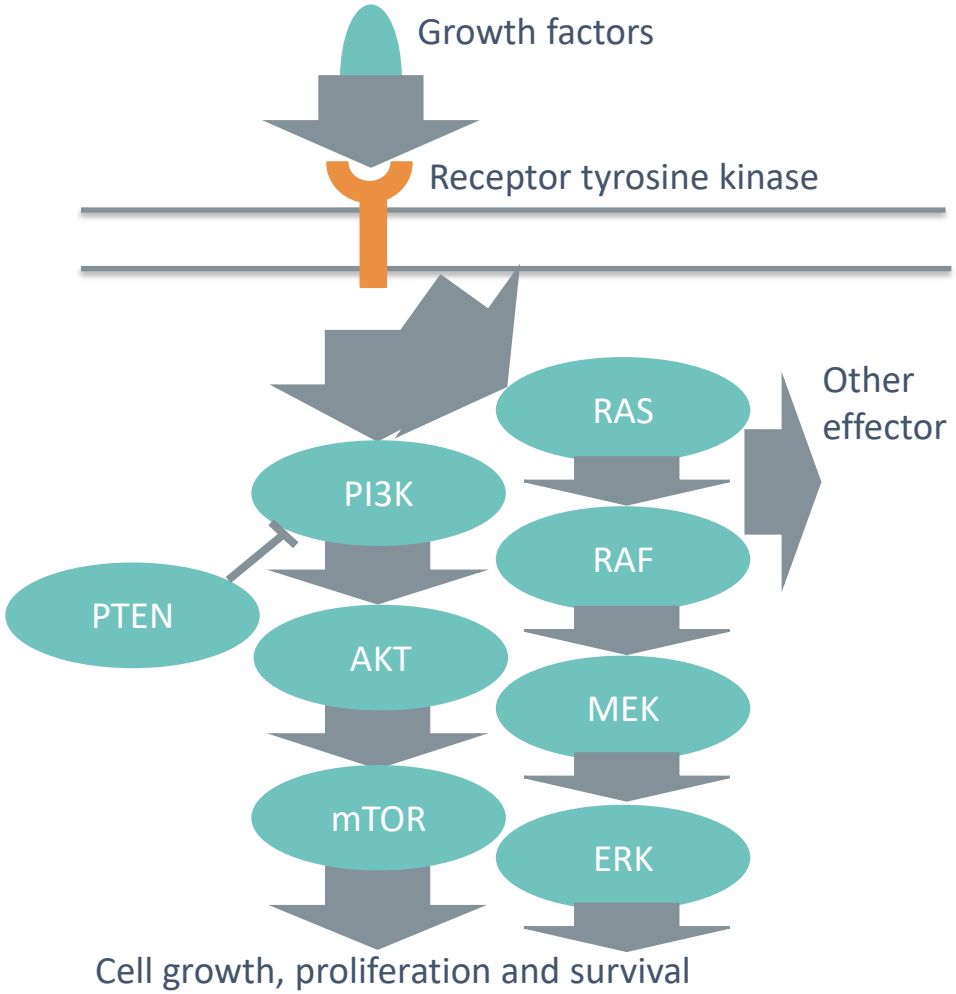
Clinical data on molecularly guided therapies studied in CCA*

Genetic Alterations	Clinical data
***ERBB2* amp, mut.**	Uncertain clinical benefit with mAbs[1]
***EGFR* mutation**	Erlotinib or cetuximab + gemcitabine + oxaliplatin has demonstrated encouraging results in phase II trials[1]
***VEGF* overexpression**	Bevacizumab + gemcitabine + oxaliplatin gave a median PFS of 7 months and OS of 12.7 months in a phase II trial[1]
***FGFR2* fusion**	Ponatinib has encouraging results in small group of patients[1], pemigatinib has shown potential therapeutic benefit[2]
***KRAS* mutation**	Case report of patient with *KRAS* mutation who achieved SD when treated with pazopanib + trametinib[3]
***BRAF* mutation**	Case report of patient with V600 mutation who achieved a CR after treatment with vemurafenib, panitumumab, irinotecan[1]
MEK	Selumetinib gave a PR in 12% and SD in 68% of patients in a phase II trial[4]
***PI3K* mutations**	mTOR inhibitor: SD in 60%[1]
***PTEN* mutations**	
***NTRK* fusions**	Tyrosine kinase inhibitor entrectinib gave an ORR of 57.4% in phase I/II trial[5]
MET	Cabozantinib has shown unsatisfactory results (PFS: 1.7 months and OS: 5.2 months); tivantinib + gemcitabine gave better results showing a PR of 20% and SD of 46%[1]



* Until now, the majority of trials focused on the targets featured in the illustration. amp: amplification; CCA: cholangiocarcinoma; CR: complete response; mAbs: monoclonal antibodies; mut: mutation; OS: overall survival; PFS: progression-free survival; PR: partial response; SD: stable disease.

Figure adapted from Similie, M.M., et al (2019) *Medicina* 55: doi: 10.3390/medicina55020042.

1. Similie, M.M., et al (2019) *Medicina* 55: doi: 10.3390/medicina55020042; 2. Abou-alfa, G.K., et al. (2020) *Lancet Oncol* doi: 10.1016/S1470-2045(20)30109-1;
3. Churi C. et al., (2014) *PLoS ONE* 9: e115383. doi: 10.1371/journal.pone.0115383; 4. Bekaii-Saab et al., (2011) *JCO* 29:2357-63; 5. Demetri G.D. et al. (2018) presented at ESMO Congress 2018, Abstract LBA17.

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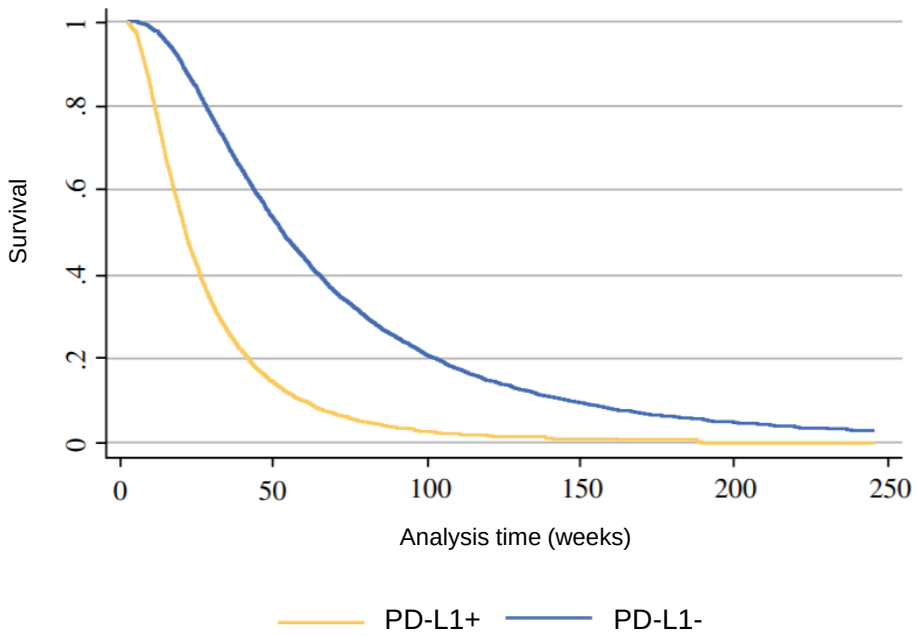
Introduction to the Rationale for Immune Checkpoint Inhibition in BTC

PD-L1 Expression is Associated with Poor Survival, Therefore PD-L1 May be a Potential Target for Treatment of BTC

Overall, studies suggest that checkpoints may be actively suppressing the host immune response in patients with BTC and could be a potential target for future therapies[1]

OS of patients undergoing surgery for ICC by PD-L1 at the tumor margin[2]



A higher ratio of PD-1-positive to CD8+ tumor-infiltrating lymphocytes were associated with **poorer OS, RFS and distant metastasis**[1]

PD-L1 expression was associated with an almost **60% worse survival** compared to those who were PD-L1 negative[1,2]

Upregulation of PD-L1/PD-1 is associated with worse outcomes due to less CD8+ T cell expression in PD-L1-positive tumors, compared to those without PD-L1/PD-1 upregulation[1]

BTC = biliary tract cancer; CD8+ = cluster of differentiation 8; ICC = Intrahepatic cholangiocarcinoma; OS = overall survival; PD-1 = programmed death protein 1; PD-L1 = programmed cell death ligand-1; RFS = recurrence-free survival.

1. Jakubowski CD, et al. *Chin Clin Oncol*. 2020;9:2; 2. Gani F, et al. *Ann Surg Oncol*. 2016;23:2610–2617.

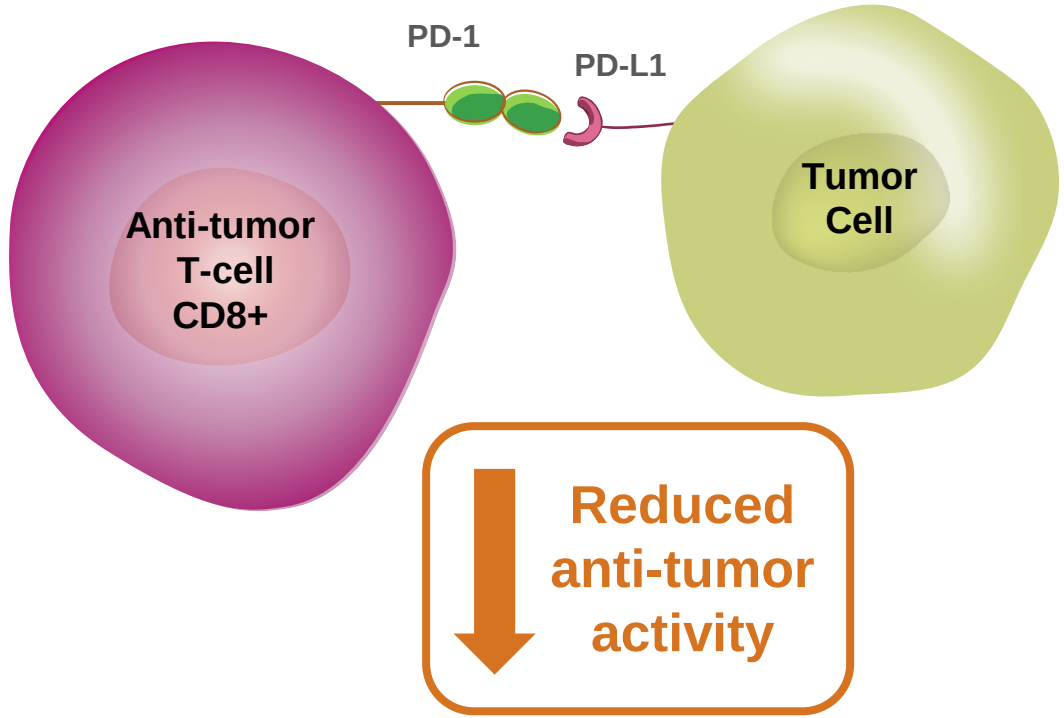
Immune Checkpoint Molecules, such as PD-L1, Expressed by Anti-tumor T Cells Mediate Immune Dysregulation Associated with BTC

An increased expression of immune checkpoints molecules, such as PD-L1, has been observed in BTC patients[1]

PD-L1 expressed on the tumor cell can **induce exhaustion** of anti-tumor T cells in the tumor microenvironment by interacting with PD-1 expressed on the anti-tumor T cell[1]

PD-L1 expression is present in the majority of BTC patients samples at baseline and is **associated with poor survival**[1]

The worst prognosis is observed in BTC patients with **hypermutated tumors and elevated gene expression of checkpoint inhibitors including PD-L1**[1]



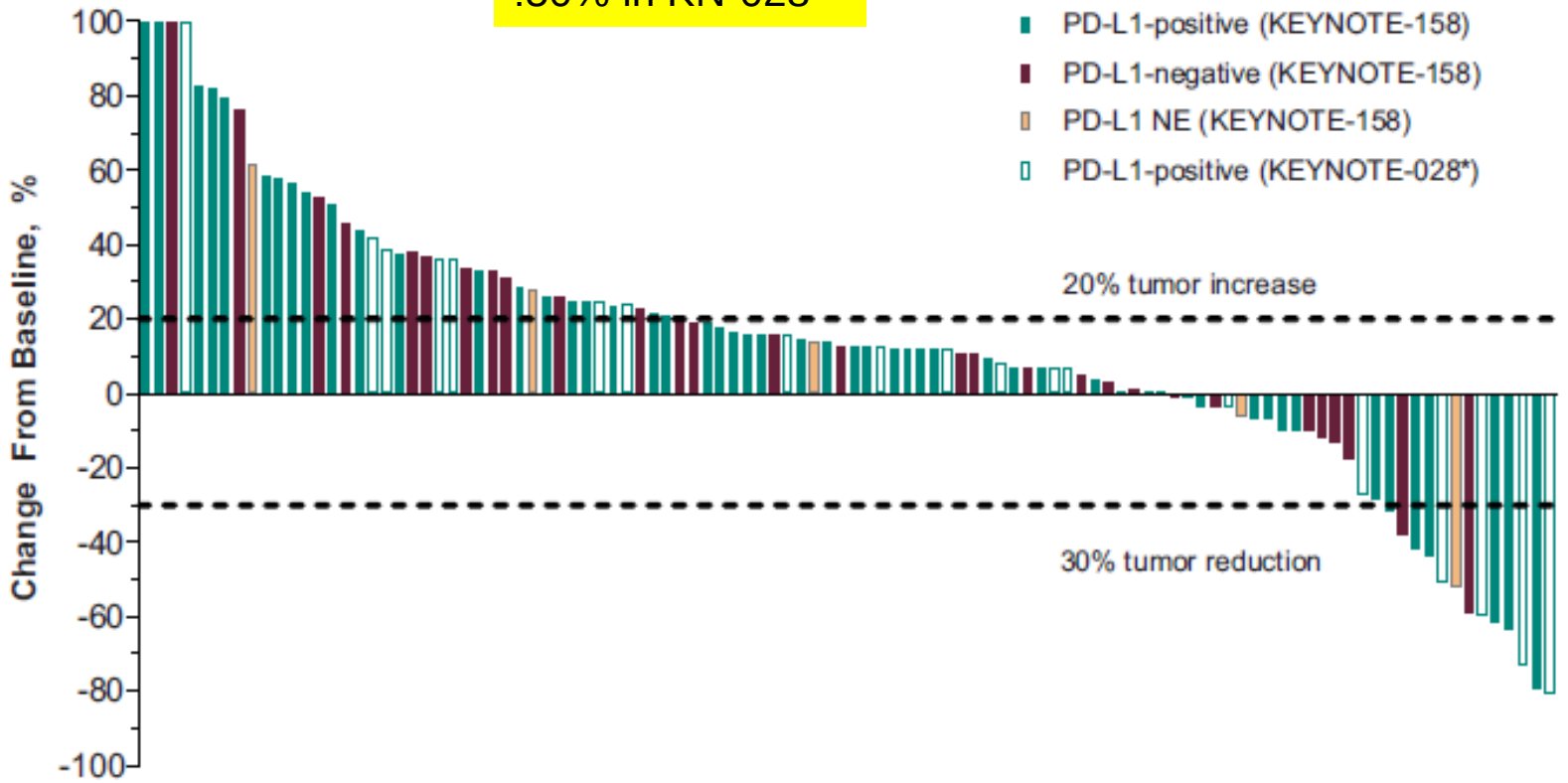
BTC = biliary tract cancer; CD8+ = cluster of differentiation 8; PD-1 = programmed death protein 1; PD-L1 = programmed cell death ligand-1.

1. Jakubowski CD & Azad NS. *Chin Clin Oncol.* 2020;9:2.

Targeting Immune Checkpoints in BTC

➢KEYNOTE-028 & 158, Pembrolizumab

≥3 L prior therapy
:23% in KN-158,
:50% in KN-028



	KEYNOTE-158 N = 104	KEYNOTE-028 N = 23
ORR,[a] % (95% CI)	5.8 (2.1–12.1)	13.0 (2.8–33.6)
Best objective response, n (%)		
CR	0	0
PR	6 (5.8)	3 (13.0)[b]
SD	17 (16.3)	3 (13.0)
PD	65 (62.5)	11 (47.8)
Non-evaluable[c]	2 (1.9)	3 (13.0)
No assessment[d]	14 (13.5)	3 (13.0)
Time to response, median (range), months[e]	2.2 (1.9–6.0)	3.5 (1.8–5.6)
DOR, median (range), months[e,f]	NR (6.2–26.6+)	NR (21.5–53.2+)
Kaplan-Meier estimate of DOR, %		
≥12 months	50.0	100
≥24 months	50.0	66.7

	PD-L1–Positive n = 61	PD-L1–Negative n = 34
ORR,[a] % (95% CI)	6.6 (1.8–15.9)	2.9 (0.1–15.3)
Best objective response, n (%)		
CR	0	0
PR	4 (6.6)	1 (2.9)
SD	6 (9.8)	11 (32.4)
PD	44 (72.1)	17 (50.0)
Non-evaluable[e]	2 (3.3)	0
No assessment[c]	5 (8.2)	5 (14.7)
PFS, median (95% CI), months	1.9 (1.8–2.0)	2.1 (1.9–2.6)
OS, median (95% CI), months	7.2 (3.7–10.8)	9.3 (4.2–11.5)

Piha-Paul SA, Oh DY, et al. Int J Cancer 2020

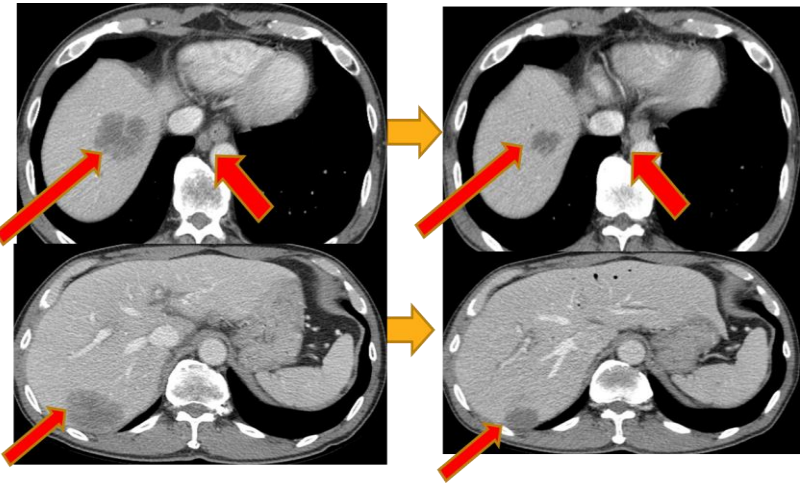
Targeting Immune Checkpoints in BTC

➢ KEYNOTE-028, Pembrolizumab, PDL1 (+) BTC

- M/58, CBD ca, M/Liver, LNs, Lung

-1L Gem/Cis #8
-2L 5FU/Adriamycin/MMC #6
-3L Pembro

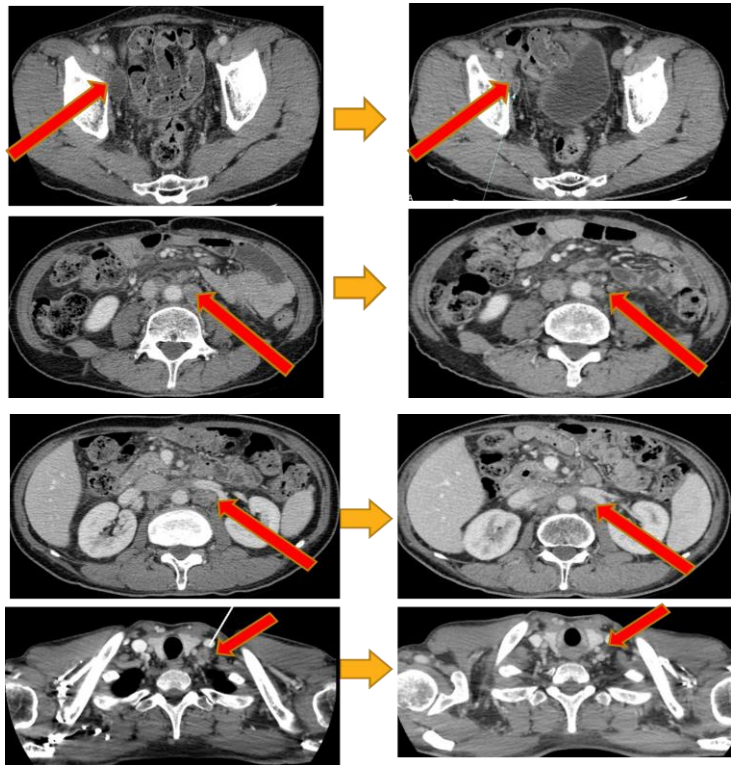
PR



- M/58, Cholangiocarcinoma, M/LNs, Lung

-1L Gem/Cis #8
-2L Capecitabine/Cis#6,
-3L Pembro

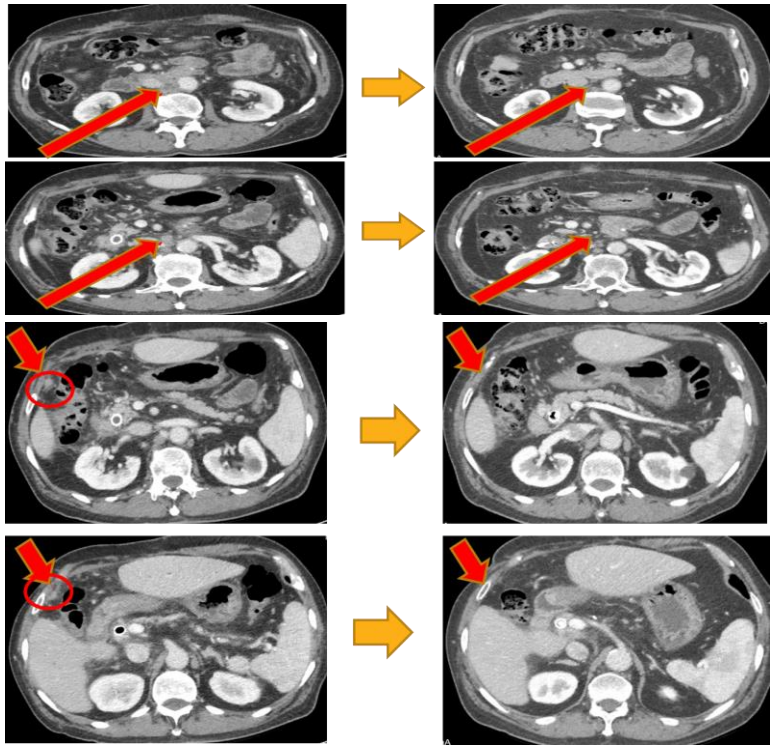
PR



- M/71, Gallbladder cancer, M/LNs, Peritoneal seeding

-1L Gem/Cis #8
-2L 5FU/Adriamycin/MMC #6
-3L Pembro

PR→CR



Targeting Immune Checkpoints in BTC

- Nivolumab, Refractory or intolerant Gem-based treatment

	Nivo mono (N=30)
OS (90% CI), mo	5.2 (4.5-8.7)
PFS (90% CI), mo	1.4 (1.4-1.4)
ORR (90% CI), %	3.3 (0.7-13.6)
PD-L1≥1%, N	6
OS	11.6
PFS	2.1
ORR, %	17
PD-L1<1%, N	23
OS	5.2
PFS	1.4
ORR, %	0

Ueno M et al. Lancet Gastroenterol Hepatol 2019

- Durvalumab with or without Tremelimumab

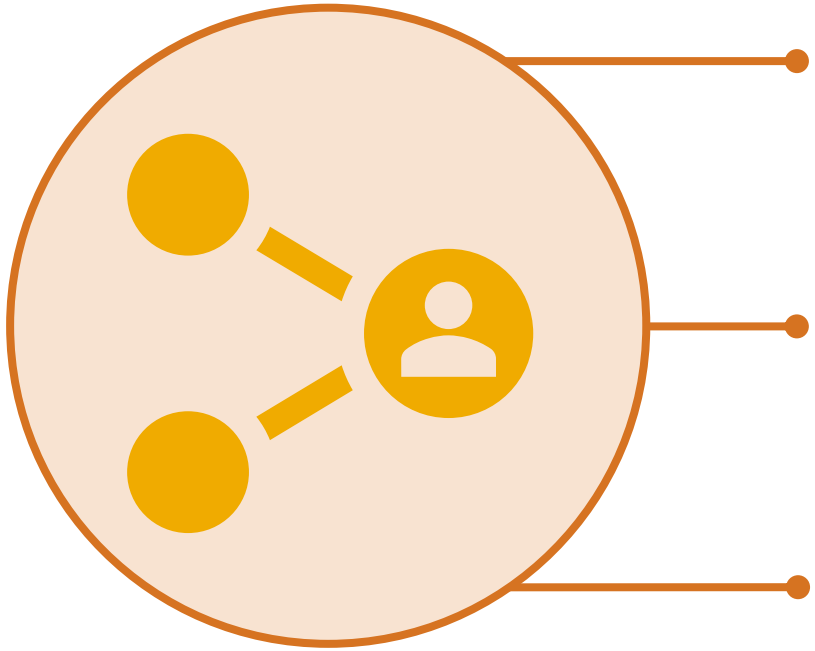
	Durvalumab (n=42)	Durvalumab +Tremelimumab (n=65)
ORR	4.8% (95% CI,0.6-16.2)	10.8% (95% CI,4.4-20.9)
PFS	1.5 m (95% CI,1.4-2.6)	1.6 m (95% CI,1.4-2.8)
OS	8.1 m (95% CI,5.6-10.2)	10.1 m (95% CI,6.2-11.4)
OS rate at 12 m	18.8%	29.3%

Doki Y, Oh DY et al. Cancer Med 2022

Introduction to the Rationale for IO + Chemotherapy in BTC

Combinational Approaches May be Essential to Break Immune Tolerance Associated with BTC

Despite the activity of anti-PD-1/PD-L1 monotherapy in BTC, combinational approaches may be essential to further improve clinical outcomes[1]



BTC express PD-L1 and **high levels of soluble PD-L1, which correlates with poor prognosis** in BTC patients treated with chemotherapy[1]

PD-L1 inhibitors such as durvalumab **in combination** with **cytotoxic chemotherapy** may contribute to a **more effective anti-tumor immune response**[1]

Having observed that **BTC is sensitive to chemotherapy**, durvalumab is being studied in combination with gemcitabine plus cisplatin in the Phase II BTC-1st MEDITREME trial and the Phase III TOPAZ-1 trial[1,2]

BTC = biliary tract cancer; PD-1 = programmed death protein 1; PD-L1 = programmed cell death ligand-1.

1. Oh D-Y, et al. Presented at ASCO 2020 Virtual Meeting. May 29-31, 2020. Poster 4520; 2. Ioka T, et al. Presentation at ASCO GU Annual Meeting; February 14-16, 2019; San Francisco, CA. Poster 387.

Rationale for Durvalumab plus Chemotherapy in BTC

New treatment strategies are required and thus several IO therapies are under investigation (such as durvalumab) in combination with existing regimens.

There is also a rationale for the use of a PD-1/PD-L1 antagonist such as durvalumab in combination with cytotoxic chemotherapy based on emerging evidence of activity of this combination in a variety of cancers.[1]

The combination of these agents may provide a complementary benefit in mounting an effective antitumor immunity by promoting antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumor bed.[2]

An immunotherapy agent that aids in the recognition of cancer cells by T cells may lead to long-lived tumor destruction, helping to prolong the early tumor responses seen with cytotoxic agents.[3]

Consequently, combination of gemcitabine and cisplatin with immune checkpoint inhibitors such as durvalumab may result in enhanced efficacy and improved outcome in BTC based on these complementary mechanisms of action (MOAs).[4]

BTC = biliary tract cancer; IO = immun-oncology; MOA = mechanism of action; PD-1 = programmed death protein 1; PD-L1 = programmed cell death ligand-1.

1. Langer CJ et al. *Lancet Oncol*. 2016; 17:1497-1508; 2. Mellamn I et al. *Nature*. 2011; 480:480-489; 3. Bracci L et al. *Cell Death Differ*. 2014; 21:15-25; 4. Vaneman M et al. *Cell Death Differ*. 2014; 21:15-25.

MediTreme Study

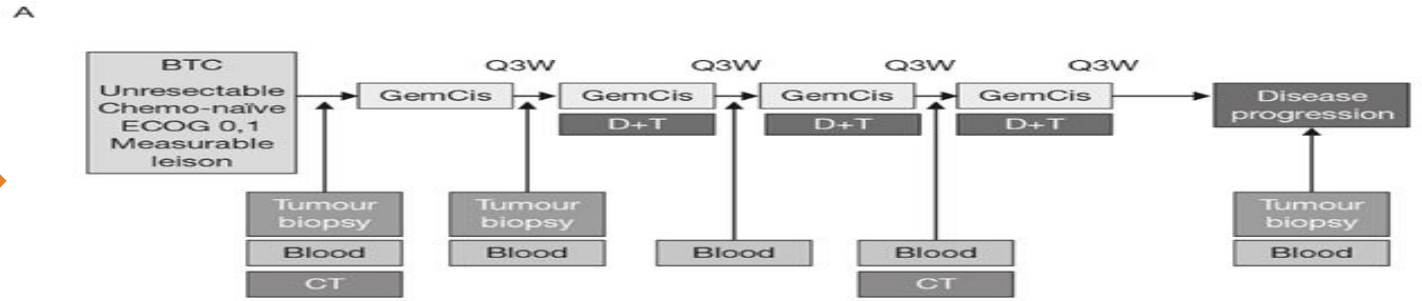
Durvalumab(MEDI4736)/Tremelimumab in Combination with Gemcitabine/Cisplatin in Treatment-naïve Korean Patients with Unresectable or Metastatic Biliary Tract Cancer

IO+Chemotherapy in BTC

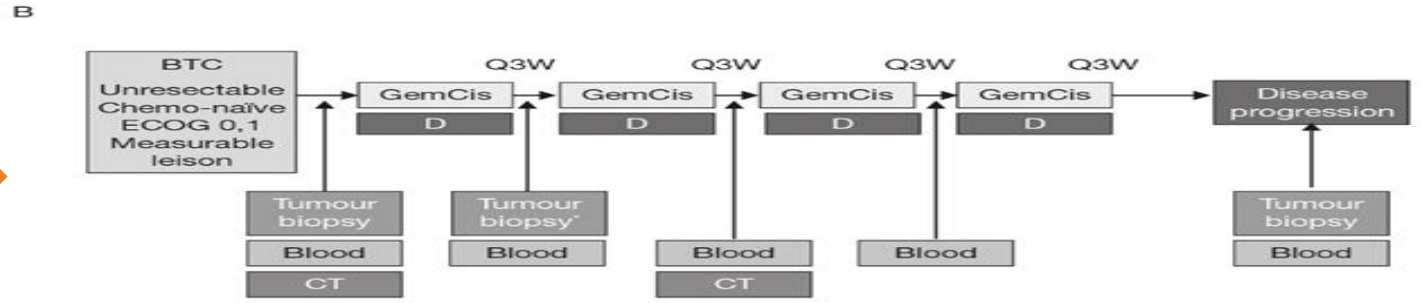
- Durvalumab+ Chemotherapy, 1L, BTC

➢BTC-1st MEDITREME

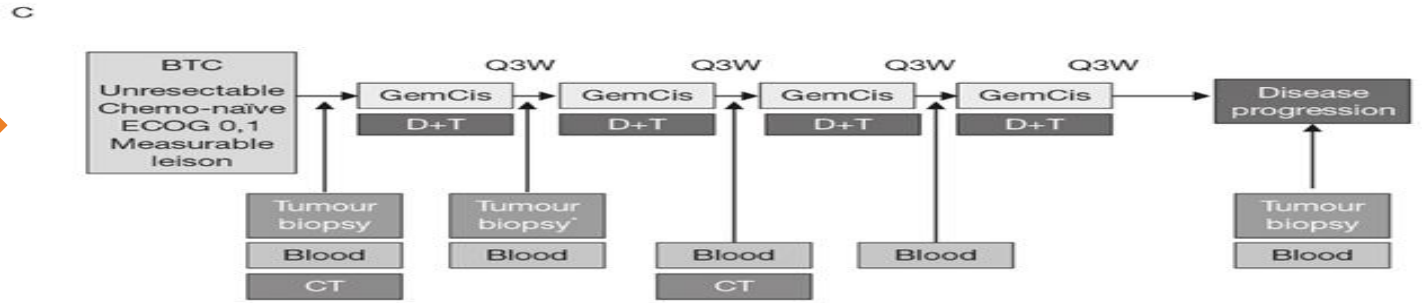
Cohort 1: GC->GC+D+T



Cohort 2: GC+D



Cohort 3: GC+D+T



GC:GemCis
D:Durvalumab,
T: Tremelimumab, maximum 4 cycles

ClinicalTrials.gov Identifier: NCT03046862

Oh DY, et al. Lancet Gastroenterol Hepatol 2022

BTC-1st MEDITREME

➢ Patient demographics and baseline characteristics in the efficacy population

	Treatment cohort			
Parameter	GC→GC+D+T (N=30)	GC+D (N=47)	GC+D+T (N=47)	Total (N=124)
Age, median (interquartile range), years	64 (57–68)	61 (57–71)	66 (60–71)	64 (58–70)
Sex, male, n (%)	17 (57)	19 (40)	25 (53)	61 (49)
ECOG performance status, n (%)				
0	30 (100)	19 (40)	23 (49)	72 (58)
1	0	28 (60)	24 (51)	52 (42)
Extent of disease, n (%)				
Initially unresectable	14 (47)	27 (57)	27 (57)	68 (55)
Recurrent	16 (53)	20 (43)	20 (43)	56 (45)
Primary tumour type, n (%)				
Intrahepatic cholangiocarcinoma	17 (57)	29 (67)	20 (43)	66 (53)
Gall bladder	7 (23)	7 (15)	16 (34)	30 (24)
Extrahepatic cholangiocarcinoma	2 (7)	9 (19)	3 (6)	14 (11)
Ampulla of Vater	4 (13)	2 (4)	8 (17)	14 (11)
Previous history of surgery, n (%)	16 (53)	28 (60)	29 (62)	73 (58)
Previous adjuvant therapy, n (%)	11 (37)	15 (32)	14 (30)	40 (32)
Interval of recurrence after adjuvant therapy, n (%)				
Not done	19 (63)	32 (68)	33 (70)	84 (67)
During	1 (3)	2 (4)	1 (2)	4 (3)
<6 months post-completion	6 (20)	8 (17)	9 (19)	23 (19)
≥6 months post-completion	4 (13)	5 (11)	4 (9)	13 (11)
Metastatic site, n (%)				
Liver	24 (80)	20 (43)	23 (49)	67 (54)
Lung	14 (47)	8 (17)	10 (21)	32 (26)

BTC-1st MEDITREME

➢ AE

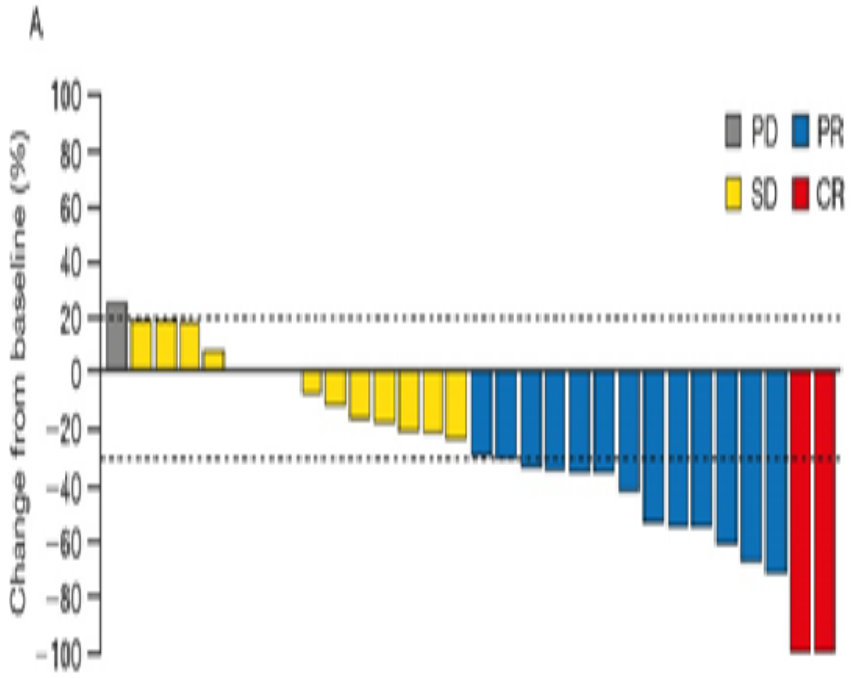
	Treatment cohort											
	GC→GC+D+T (N=32)			GC+D (N=47)			GC+D+T (N=47)			Total (N=126)		
Adverse event, n (%)	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Haematologic												
Neutrophil count decreased	19 (59)	12 (38)	5 (16)	28 (60)	18 (40)	9 (19)	25 (53)	19 (40)	4 (9)	72 (57)	49 (39)	18 (14)
Anaemia	18 (56)	13 (41)	0	22 (47)	17 (36)	2 (4)	19 (40)	18 (38)	0	59 (47)	48 (38)	2 (2)
Platelet count decreased	13 (41)	3 (9)	1 (3)	16 (34)	7 (15)	2 (4)	16 (34)	9 (19)	2 (4)	45 (36)	19 (15)	5 (4)
Non-haematologic												
Nausea	22 (69)	1 (3)	0	32 (68)	0	0	22 (48)	0	0	78 (62)	1 (1)	0
Pruritis	22 (69)	0	0	26 (55)	0	0	25 (53)	0	0	73 (58)	0	0
Anorexia	26 (81)	1 (3)	0	21 (45)	0	0	20 (43)	0	0	67 (53)	1 (1)	0
Fatigue	21 (66)	0	0	18 (38)	0	1 (2)	20 (43)	0	0	59 (47)	0	1 (1)
Fever	13 (41)	1 (3)	0	15 (32)	0	0	21 (44)	0	0	49 (39)	1 (1)	0
Papulopustular rash	13 (41)	0	0	14 (30)	0	0	25 (53)	0	0	52 (41)	0	0
Constipation	8 (25)	0	0	23 (49)	0	0	20 (43)	0	0	51 (40)	0	0
Vomiting	11 (34)	1 (3)	0	19 (40)	0	0	14 (30)	0	0	44 (35)	1 (1)	0
Diarrhoea	7 (22)	0	0	11 (23)	2 (4)	0	13 (28)	2 (4)	0	31 (25)	4 (3)	0
Peripheral sensory neuropathy	9 (28)	0	0	14 (30)	0	0	10 (21)	0	0	33 (26)	0	0
Weakness	9 (28)	1 (3)	0	5 (11)	0	0	9 (19)	2 (4)	0	23 (18)	3 (2)	0
AST/ALT elevated	2 (6)	2 (6)	0	6 (13)	1 (2)	0	4 (9)	0	0	12 (10)	3 (2)	0
Stomatitis	7 (22)	0	0	3 (6)	0	0	4 (9)	0	0	14 (11)	0	0
Blood bilirubin increased	1 (3)	0	0	5 (11)	0	1 (2)	5 (11)	3 (6)	0	11 (9)	3 (2)	1 (1)
Infection	1 (3)	0	0	2 (4)	2 (4)	0	5 (11)	1 (2)	1 (2)	8 (6)	3 (2)	1 (1)
Cholangitis	0	0	0	4 (9)	4 (9)	0	3 (6)	3 (6)	0	7 (6)	7 (6)	0
Thromboembolic event	2 (6)	2 (6)	0	0	0	0	4 (9)	4 (9)	0	6 (5)	6 (5)	0
Creatinine increased	2 (6)	1 (3)	0	3 (6)	0	0	1 (2)	0	0	6 (5)	1 (1)	0
Hypertension	2 (6)	1 (3)	0	2 (4)	1 (2)	0	0	0	0	4 (3)	2 (2)	0
Hyperglycaemia	2 (6)	2 (6)	0	0	0	0	0	0	0	2 (2)	2 (2)	0
Adrenal insufficiency	0	0	0	1 (2)	1 (2)	0	1 (2)	0	0	2 (2)	1 (1)	0
GGT elevation	1 (3)	0	1 (3)	0	0	0	0	0	0	1 (1)	0	1 (1)

Oh DY, et al. Lancet Gastroenterol Hepatol 2022

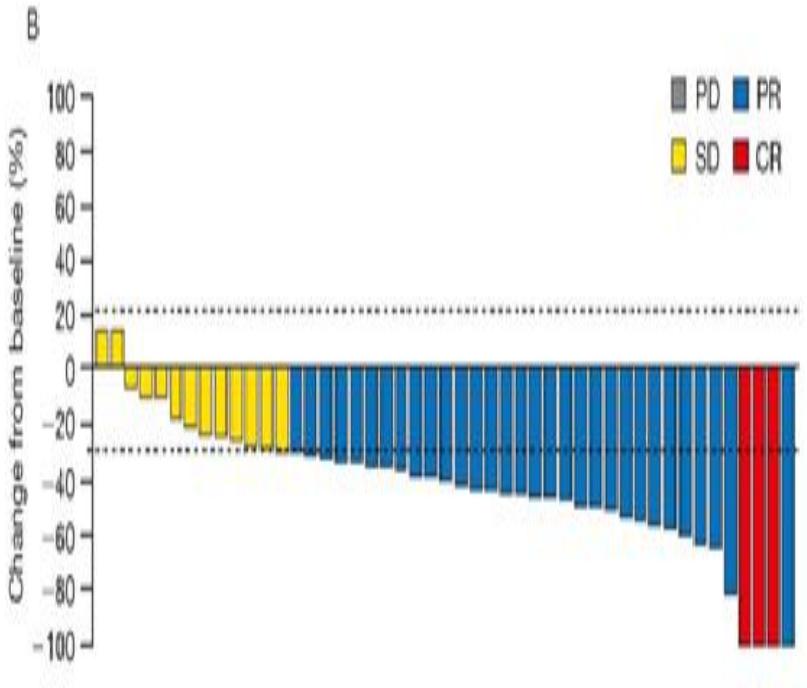
BTC-1st MEDITREME

- Treatment response

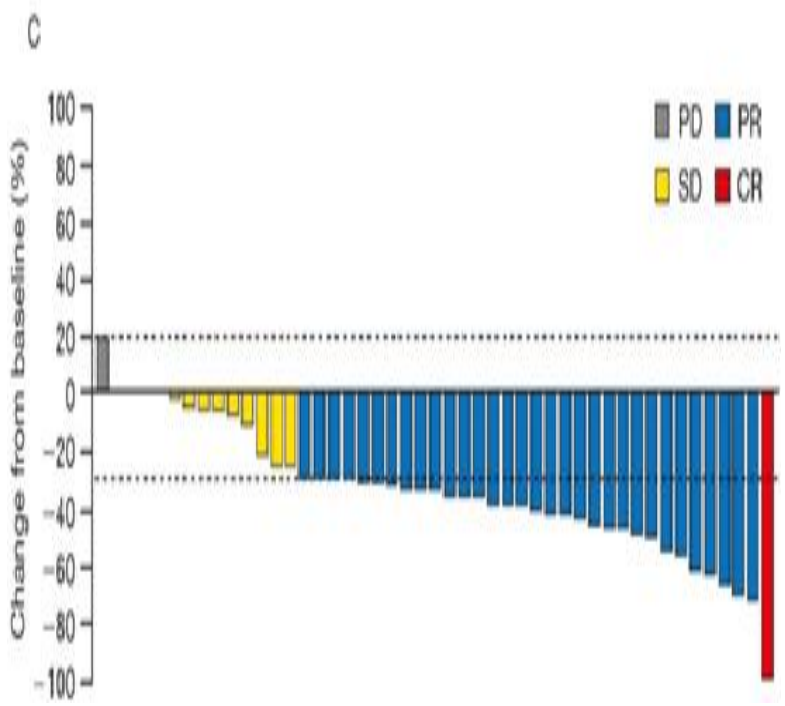
Cohort 1: GC->GC+D+T



Cohort 2: GC+D



Cohort 3: GC+D+T



Oh DY, et al. Lancet Gastroenterol Hepatol 2022

BTC-1st MEDITREME

➢ Treatment response

	Treatment cohort			
Tumour response	**GC→GC+D+T (N=30)**	**GC+D (N=47)**	**GC+D+T (N=47)**	**Total (N=124)**
Complete response, n (%; 95% CI)	2 (7; 2–21)	3 (6; 2–17)	1 (2; 0–11)	6 (5; 2–10)
Partial response, n (%; 95% CI)	13 (43; 27–61)	31 (66; 52–78)	32 (68; 54–80)	76 (61; 53–69)
Stable disease, n (%; 95% CI)	14 (47; 30–64)	13 (28; 17–42)	13 (28; 17–42)	40 (32; 25–41)
Progressive disease, n (%; 95% CI)	1 (3; 0–17)	0 (0; 0–8)	1 (2; 0–11)	2 (2; 0–6)
Objective response rate, % (95% CI)	**50 (33–67)**	**72 (58–83)**	**70 (56–81)**	**66 (57–74)**
Disease control rate, % (95% CI)	97 (83–100)	100 (92–100)	98 (89–100)	98 (94–100)
Time to onset of response, median (interquartile range), months	2·8 (2·0–6·3)	1·5 (1·3–3·2)	2·1 (1·4–4·3)	2·3 (1·4–4·1)
Duration of response, median (interquartile range), months	**9·4 (4·0–20·1)**	**11·4 (8·5–19·3)**	**8·2 (5·4–17·7)**	**9·8 (6·2–18·9)**

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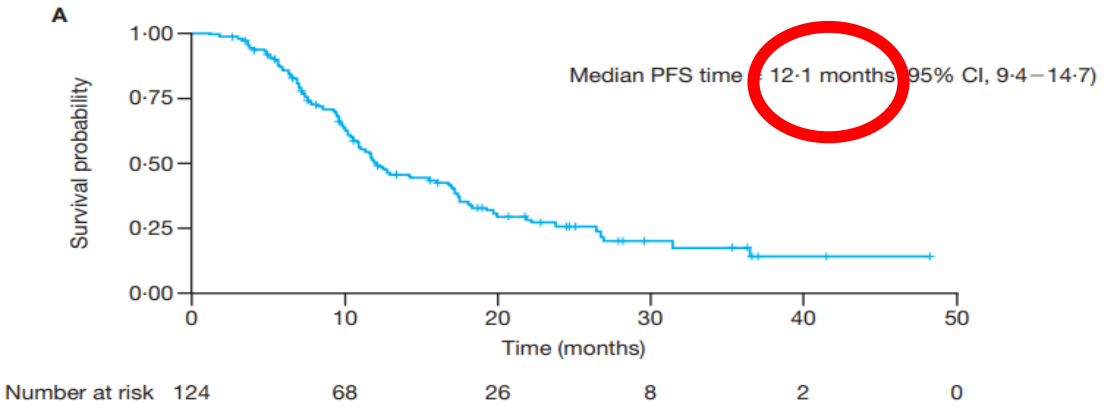
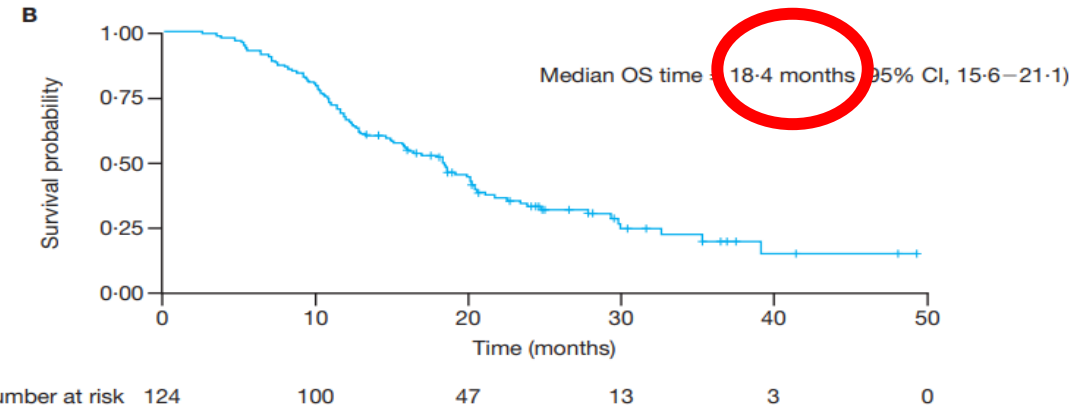
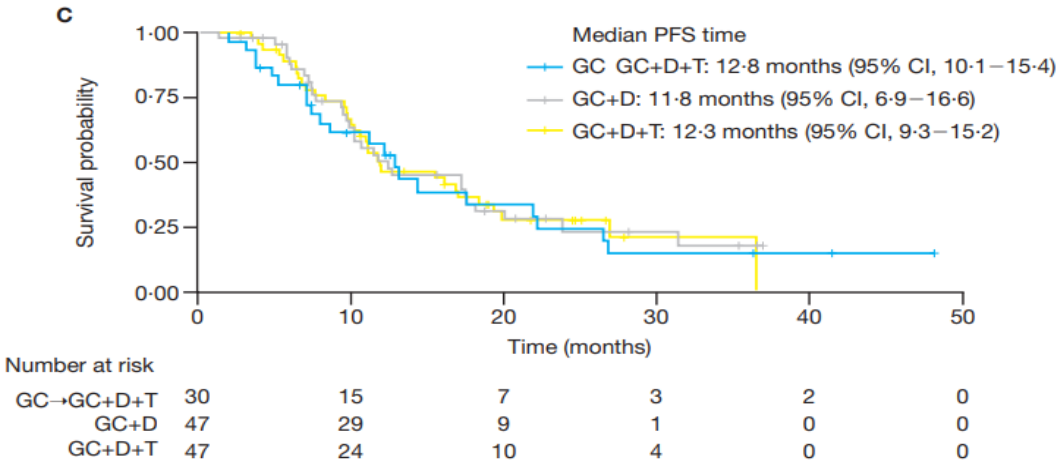
BTC-1st MEDITREME

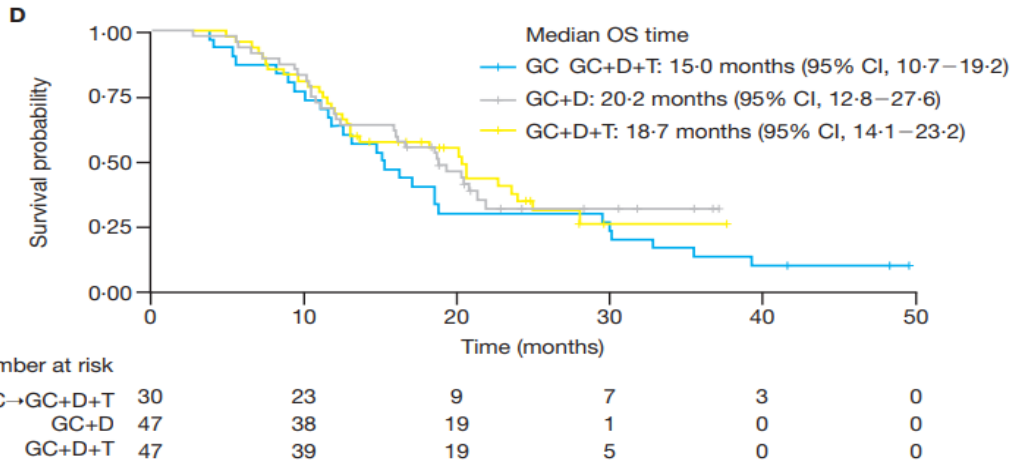
➢ PFS



➢ OS







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1992 Mercury Topaz 4 Dr GS

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1)
N=685

Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → **Durvalumab 1500 mg Q4W until PD**

Placebo Q3W + GemCis (up to 8 cycles) → **Placebo Q4W until PD**

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

Oh DY, et al. ASCO GI 2022

Patient demographics and baseline characteristics

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	17 (5.0)	12 (3.5)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status at randomization, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis,* n (%)		
Metastatic	303 (88.9)	286 (83.1)
Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression,* n (%)		
TAP ≥1%	197 (57.8)	205 (59.6)
TAP <1%	103 (30.2)	103 (29.9)

*Data missing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

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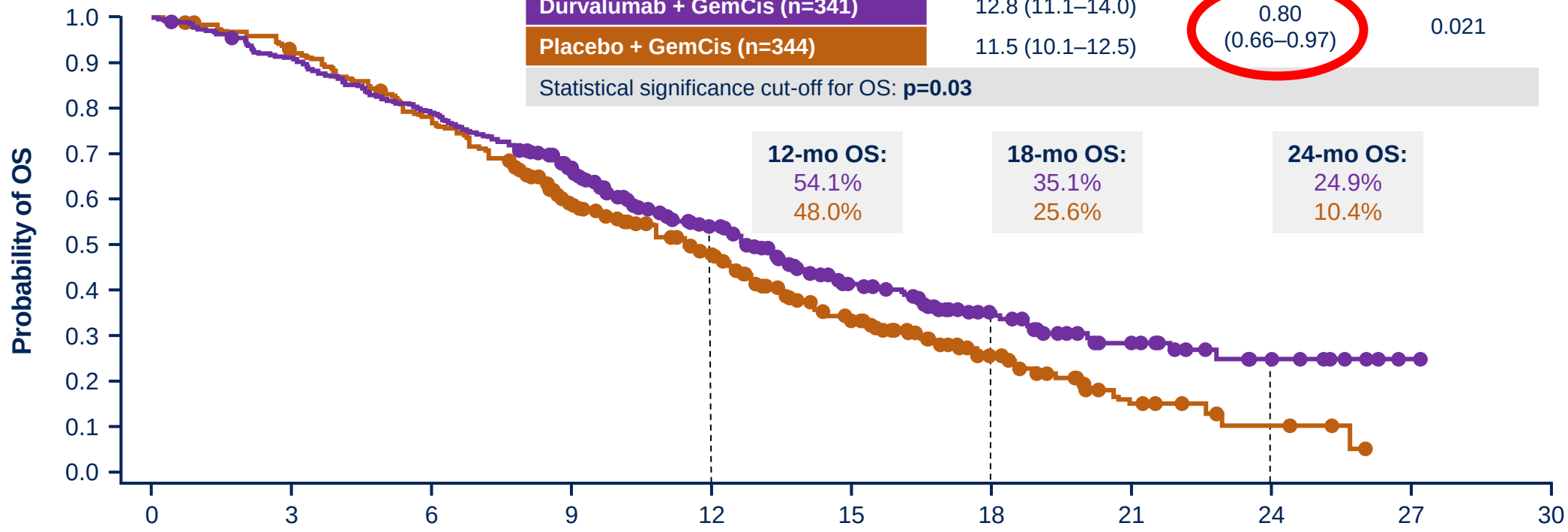
Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		

Statistical significance cut-off for OS: **p=0.03**



Number of subjects at risk

Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.

CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

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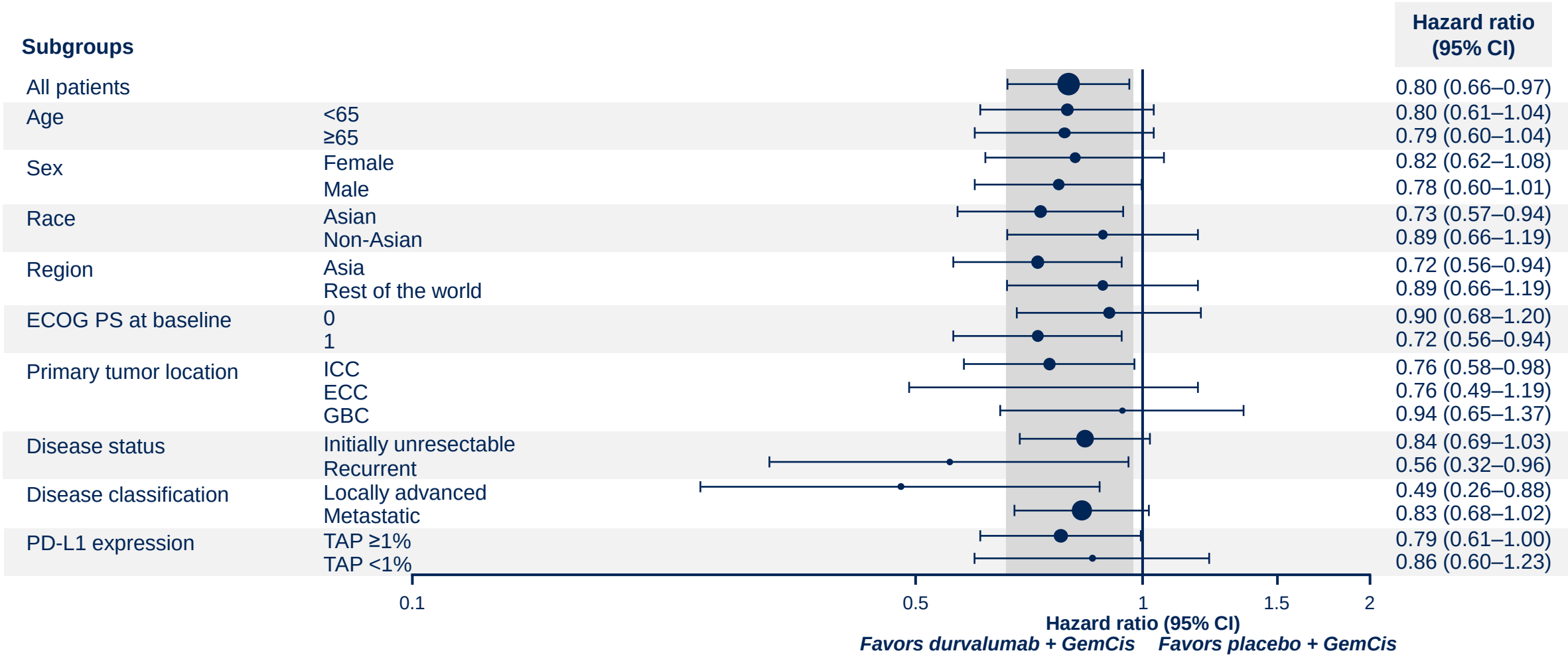
Subgroup analysis of OS



CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

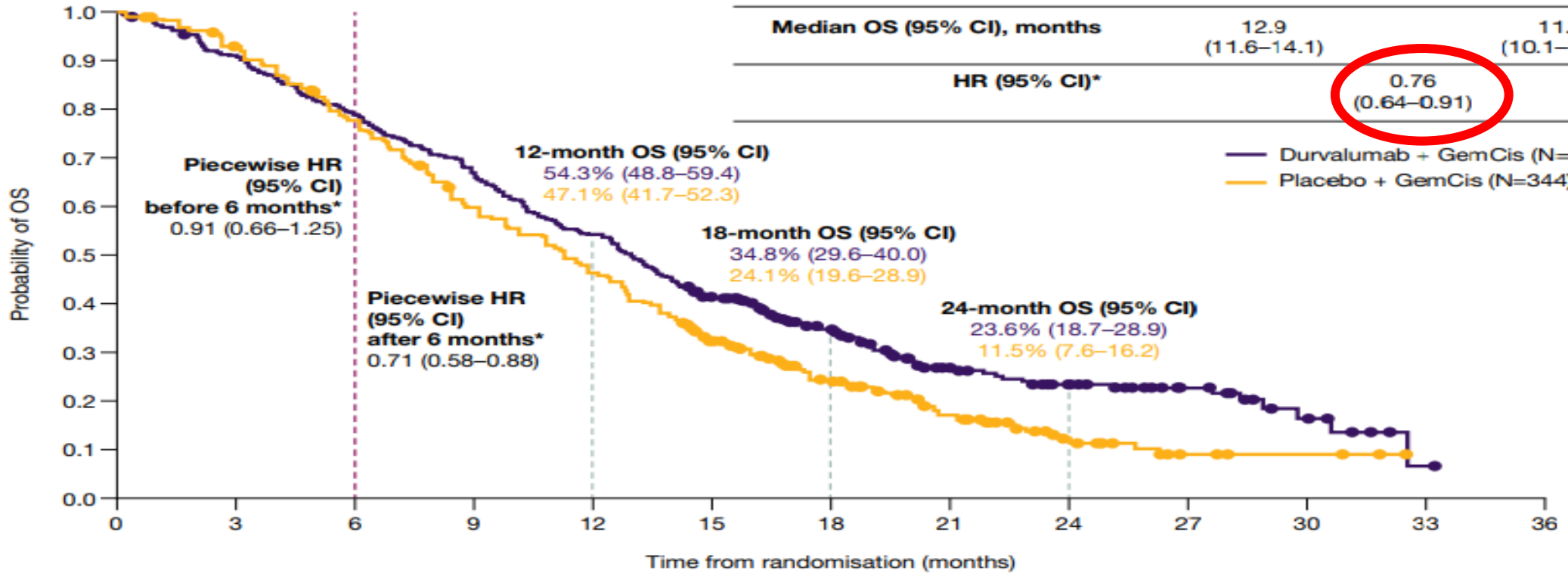
Oh DY, et al. NEJM Evidence 2022

Long-term FU (+6.5 months more FU)

Data cut-off: 25 Feb 2022
OS event maturity: 76.9%

- Overall Survival

	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=344)
Median OS (95% CI), months	12.9 (11.6–14.1)	11.3 (10.1–12.5)
HR (95% CI)*	0.76 (0.64–0.91)	



No. at risk

Durvalumab + GemCis	341	331	324	309	294	278	268	252	240	227	208	194	184	169	152	134	117	96	88	74	61	52	47	44	36	33	27	21	17	10	8	5	3	1	0
Placebo + GemCis	344	337	329	316	298	282	260	241	222	198	187	175	158	138	125	104	92	76	65	53	47	37	29	21	14	11	9	5	3	3	3	2	1	0	0

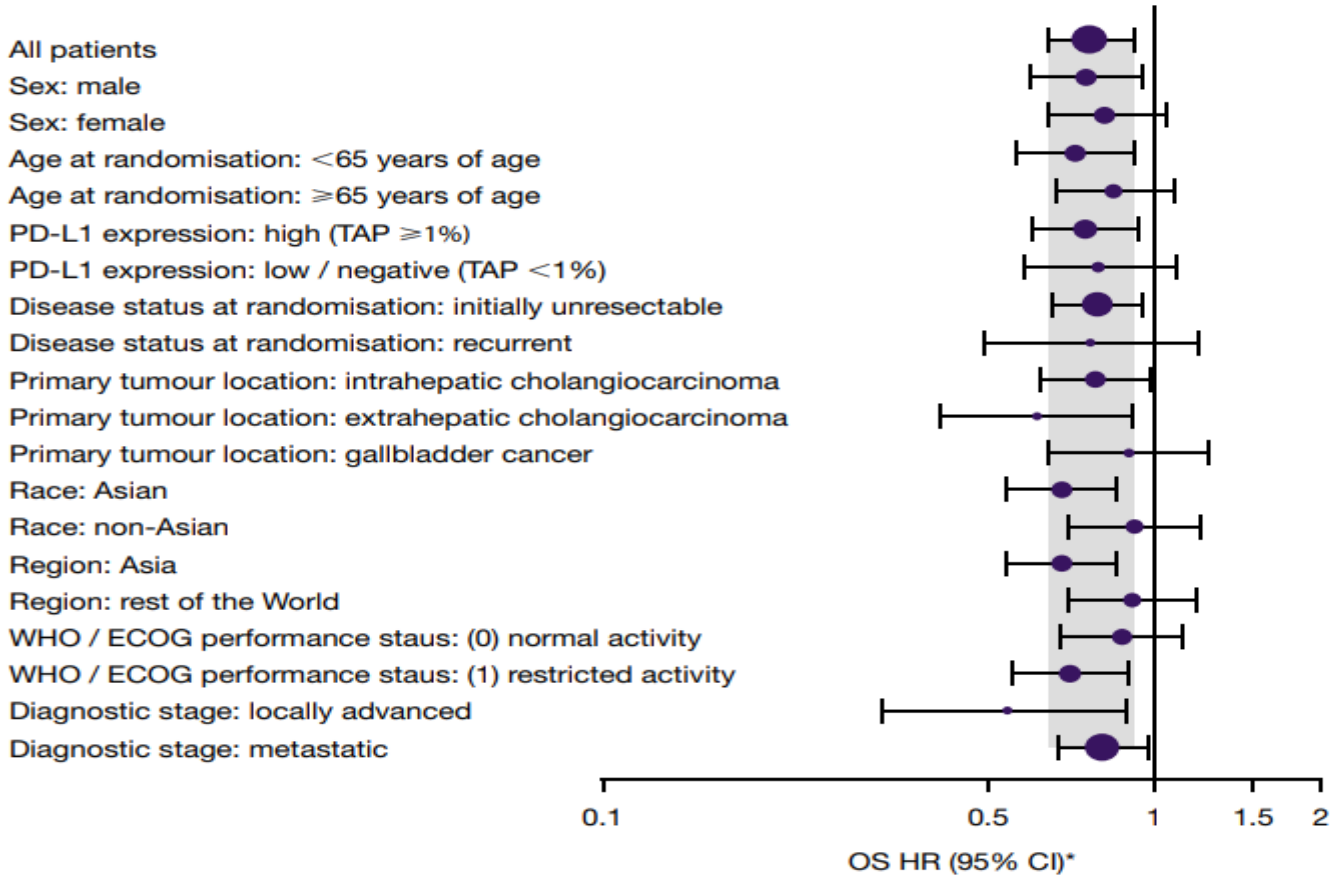
*Durvalumab + GemCis versus placebo + GemCis. An HR <1 favours durvalumab + GemCis
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; OS, overall survival

Oh DY, et al. ESMO 2022

Long-term FU (+6.5 months more FU)

Data cut-off: 25 Feb 2022
OS event maturity: 76.9%

- Subgroup analysis of Overall Survival



	Durvalumab + GemCis n/N (%)	Placebo + GemCis n/N (%)	OS HR* (95% CI)
All patients	248 / 341 (72.7)	279 / 344 (81.1)	0.76 (0.64–0.91)
Sex: male	126 / 169 (74.6)	148 / 176 (84.1)	0.75 (0.59–0.95)
Sex: female	122 / 172 (70.9)	131 / 168 (78.0)	0.81 (0.64–1.04)
Age at randomisation: <65 years of age	123 / 181 (68.0)	150 / 184 (81.5)	0.72 (0.56–0.91)
Age at randomisation: ⩾65 years of age	125 / 160 (78.1)	129 / 160 (80.6)	0.84 (0.66–1.08)
PD-L1 expression: high (TAP ⩾1%)	149 / 199 (74.9)	172 / 207 (83.1)	0.75 (0.60–0.93)
PD-L1 expression: low / negative (TAP <1%)	71 / 103 (68.9)	81 / 103 (78.6)	0.79 (0.58–1.09)
Disease status at randomisation: initially unresectable	209 / 274 (76.3)	240 / 279 (86.0)	0.79 (0.65–0.95)
Disease status at randomisation: recurrent	39 / 67 (58.2)	39 / 64 (60.9)	0.76 (0.49–1.20)
Primary tumour location: intrahepatic cholangiocarcinoma	136 / 190 (71.6)	153 / 193 (79.3)	0.78 (0.62–0.99)
Primary tumour location: extrahepatic cholangiocarcinoma	45 / 66 (68.2)	55 / 65 (84.6)	0.61 (0.41–0.91)
Primary tumour location: gallbladder cancer	67 / 85 (78.8)	71 / 86 (82.6)	0.90 (0.64–1.25)
Race: Asian	134 / 185 (72.4)	174 / 201 (86.6)	0.68 (0.54–0.85)
Race: non-Asian	114 / 156 (73.1)	105 / 143 (73.4)	0.92 (0.70–1.20)
Region: Asia	130 / 178 (73.0)	170 / 196 (86.7)	0.68 (0.54–0.85)
Region: rest of the World	118 / 163 (72.4)	109 / 148 (73.6)	0.91 (0.70–1.18)
WHO / ECOG performance staus: (0) normal activity	126 / 173 (72.8)	125 / 163 (76.7)	0.87 (0.68–1.12)
WHO / ECOG performance staus: (1) restricted activity	122 / 168 (72.6)	154 / 181 (85.1)	0.70 (0.55–0.89)
Diagnostic stage: locally advanced	22 / 38 (57.9)	45 / 57 (78.9)	0.54 (0.32–0.88)
Diagnostic stage: metastatic	226 / 303 (74.6)	234 / 286 (81.8)	0.80 (0.67–0.97)

*Durvalumab + GemCis versus placebo + GemCis. An HR <1 favours durvalumab + GemCis

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand-1; TAP, tumour area positivity; WHO, World Health Organization

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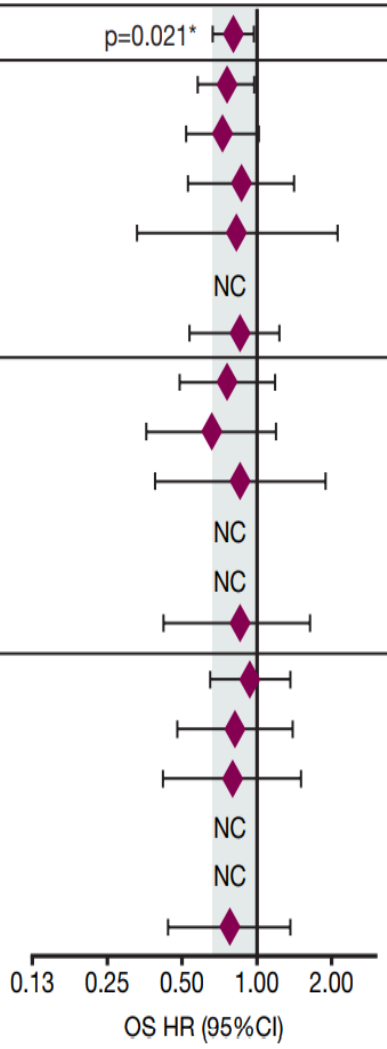
Anatomical subtype



	Durvalumab + GemCis (N=341)		Placebo + GemCis (N=344)		
	Events, n/N (%)	Median OS (95% CI), mo	Events, n/N (%)	Median OS (95% CI), mo	OS HR† (95% CI)
Full analysis set[6] p=0.021*	**198/341 (58.1)**	**12.8 (11.1–14.0)**	**226/344 (65.7)**	**11.5 (10.1–12.5)**	**0.80 (0.66–0.97)‡**
Intrahepatic cholangiocarcinoma	**105/190 (55.3)**	**13.5 (11.9–15.1)**	**126/193 (65.3)**	**11.5 (9.8–12.8)**	**0.76 (0.58–0.98)§**
Asia	60/100 (60.0)	13.0 (9.8–14.6)	81/111 (73.0)	11.4 (9.2–12.5)	0.73 (0.52–1.02)§
Europe	31/61 (50.8)	13.5 (9.5–18.8)	35/61 (57.4)	14.0 (8.0–18.3)	0.87 (0.53–1.42)§
North America	11/21 (52.4)	15.1 (6.8–NC)	9/18 (50.0)	13.3 (5.3–NC)	0.83 (0.33–2.12)§
South America	3/8 (37.5)	NR (2.3–NC)	1/3 (33.3)	NR (8.0–NC)	NC‖
Europe + North America	*42/82 (51.2)*	*13.7 (10.9–18.1)*	*44/79 (55.7)*	*13.6 (8.5–17.7)*	*0.85 (0.55–1.30)§*
Extrahepatic cholangiocarcinoma	**38/66 (57.6)**	**12.7 (9.8–16.6)**	**42/65 (64.6)**	**12.1 (7.8–14.4)**	**0.76 (0.49–1.19)§**
Asia	18/35 (51.4)	16.6 (12.6–NC)	27/42 (65.3)	12.8 (7.7–17.3)	0.66 (0.36–1.20)§
Europe	14/23 (60.9)	9.1 (8.7–NC)	12/19 (63.2)	14.4 (7.0–NC)	0.86 (0.39–1.90)§
North America	5/6 (83.3)	11.0 (0.9–NC)	3/4 (75.0)	9.6 (3.4–NC)	NC‖
South America	1/2 (50.0)	NR (10.0–NC)	0	NR	NC‖
Europe + North America	*19/29 (65.5)*	*9.8 (8.7–16.2)*	*15/23 (65.2)*	*12.1 (7.0–14.4)*	*0.86 (0.43–1.73)§*
Gallbladder cancer	**55/85 (64.7)**	**10.7 (8.9–132.)**	**58/86 (67.4)**	**11.0 (8.7–12.8)**	**0.94 (0.65–1.37)§**
Asia	25/43 (58.1)	13.3 (9.0–20.1)	29/43 (67.4)	12.6 (8.4–17.7)	0.82 (0.48–1.40)§
Europe	18/24 (75.0)	9.6 (5.2–11.1)	22/27 (81.5)	8.1 (4.9–11.0)	0.80 (0.42–1.51)§
North America	5/10 (50.0)	12.2 (2.6–NC)	4/6 (66.7)	10.2 (5.7–NC)	NC‖
South America	7/8 (87.5)	8.1 (0.9–NC)	3/10 (30.0)¶	NR (2.0–NC)	NC‖
Europe + North America	*23/34 (67.6)*	*10.3 (6.6–12.2)*	*26/33 (78.8)*	*8.7 (6.0–11.0)*	*0.78 (0.44–1.37)§*

He, et al. WCGI 2022

Long-term FU

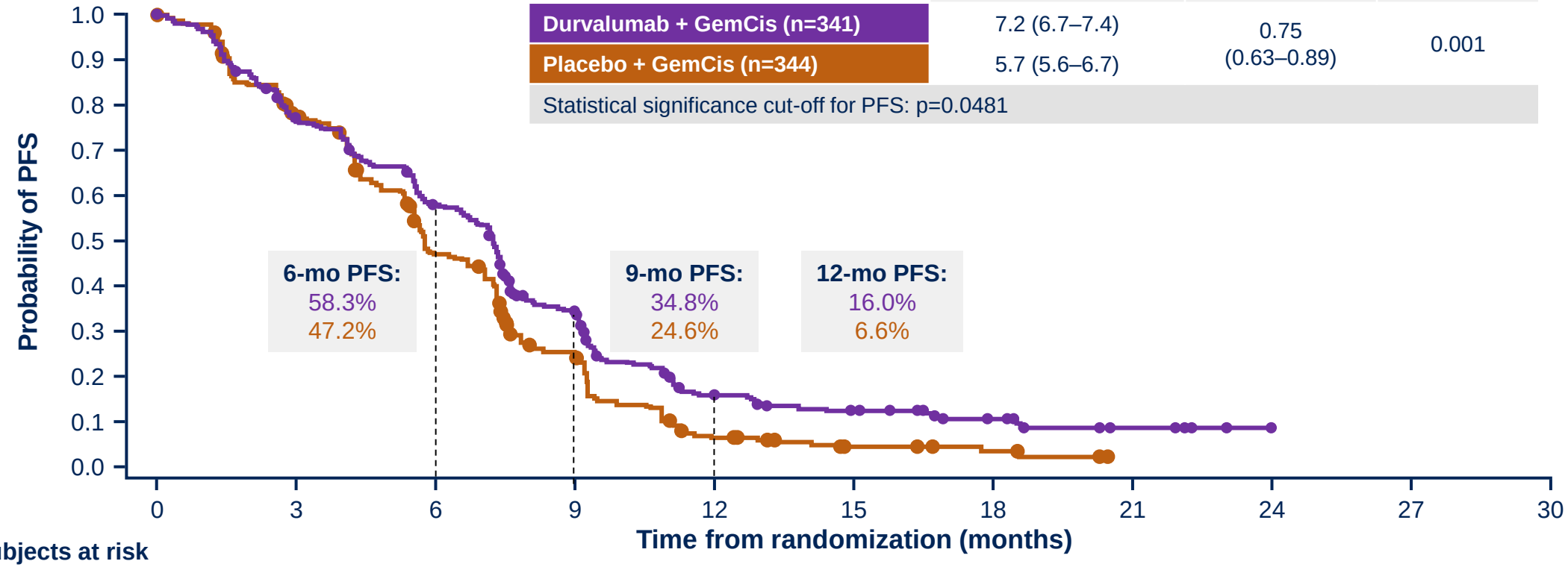
IHCC
0.78 (0.62-0.99)
vs
EHCC
0.61 (0.41-0.91)
Vs
GB
0.90 (0.64-1.25)

Oh DY, et al. ESMO 2022

Secondary endpoint: PFS

	Median PFS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + GemCis (n=344)	5.7 (5.6–6.7)		

Statistical significance cut-off for PFS: p=0.0481



Number of subjects at risk

Durvalumab + GemCis	341	258	189	100	38	25	15	5	0
Placebo + GemCis	344	255	149	71	17	7	4	0	0

Median duration of follow-up (95% CI) was 9.2 (0.0–24.0) months with durvalumab + GemCis and 6.9 (0.0–20.4) months with placebo + GemCis.

CI, confidence interval; GemCis, gemcitabine and cisplatin; PFS, progression-free survival.

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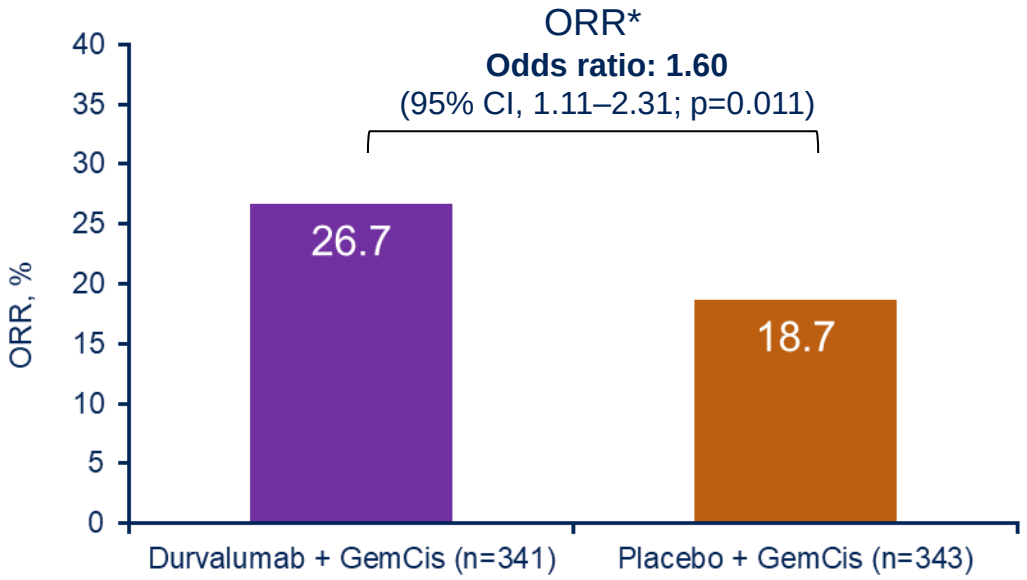
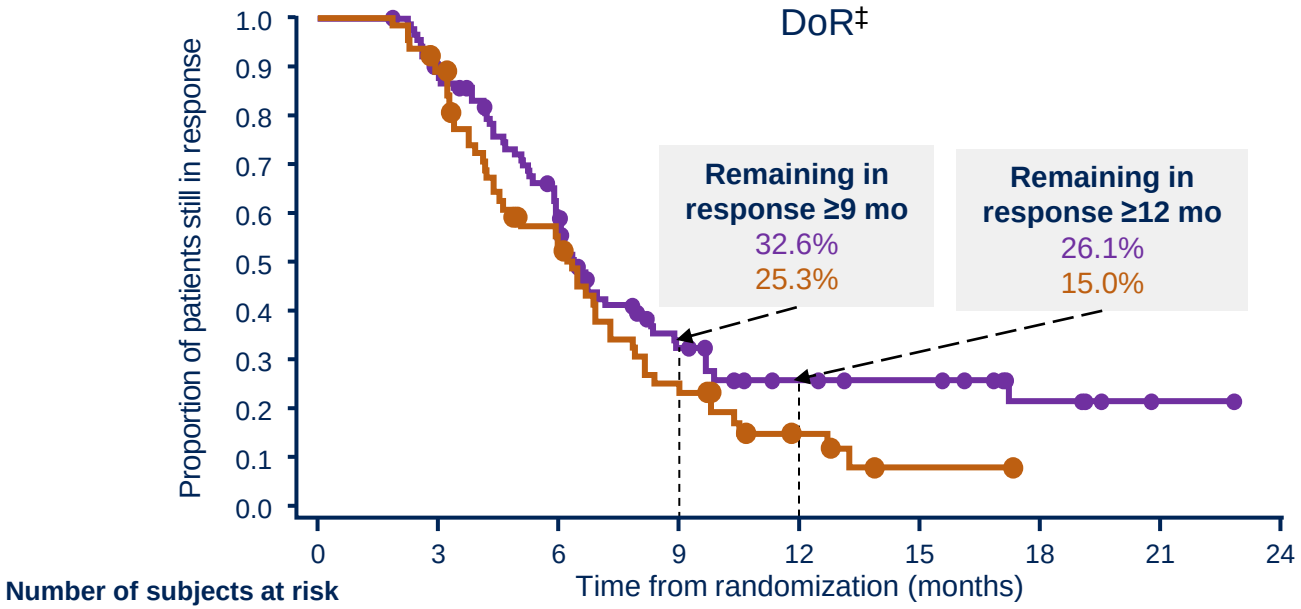
Secondary endpoint: Tumor response



	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)



	Durvalumab + GemCis (n=91)	Placebo + GemCis (n=64)
Median DoR (quartile 1–3), months	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Median time to response (quartile 1–3), months	1.6 (1.3–3.0)	2.7 (1.4–4.1)

*By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. †Analysis of DCR was based on all patients in the full analysis set. ‡Analysis of DoR was based on patients in the full analysis set who had an objective response and measurable disease at baseline.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; GemCis, gemcitabine and cisplatin; mo, month; ORR, objective response rate; PR, partial response.

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Summary of AEs and treatment exposure

	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median duration of exposure (range), months		
Durvalumab/placebo	7.33 (0.1–24.5)	5.77 (0.2–21.5)
Gemcitabine	5.19 (0.1–8.3)	5.03 (0.2–8.6)
Cisplatin	5.13 (0.1–8.3)	4.88 (0.2–8.5)
Adverse event, n (%)		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)	308 (90.1)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)
Any serious AE	160 (47.3)	149 (43.6)
Any serious TRAE	53 (15.7)	59 (17.3)
Any AE leading to discontinuation	44 (13.0)	52 (15.2)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any AE leading to death	12 (3.6)	14 (4.1)
Any TRAE leading to death	2 (0.6)	1 (0.3)
Any immune-mediated AE	43 (12.7)	16 (4.7)

Includes AEs with onset date on or after the date of the first dose or AEs that worsened after the first dose. Includes AEs occurring up to 90 days following the date of the last dose or up to the first subsequent therapy.

AE, adverse event; GemCis, gemcitabine and cisplatin; TRAE, treatment-related adverse event.

Oh DY, et al. NEJM Evidence 2022

Grade 3/4 AEs

Event, n (%)	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Any grade 3/4 AE (≥5%)		
Anemia	80 (23.7)	77 (22.5)
Neutrophil count decreased	71 (21.0)	88 (25.7)
Neutropenia	68 (20.1)	72 (21.1)
Platelet count decreased	33 (9.8)	29 (8.5)
Cholangitis	22 (6.5)	11 (3.2)
Thrombocytopenia	16 (4.7)	18 (5.3)
White blood cell count decreased	15 (4.4)	20 (5.8)
Any grade 3/4 TRAE (≥2%)		
Neutrophil count decreased	70 (20.7)	87 (25.4)
Neutropenia	65 (19.2)	69 (20.2)
Anemia	64 (18.9)	64 (18.7)
Platelet count decreased	27 (8.0)	26 (7.6)
White blood cell count decreased	14 (4.1)	20 (5.8)
Thrombocytopenia	12 (3.6)	18 (5.3)
Fatigue	9 (2.7)	8 (2.3)
Leukopenia	7 (2.1)	2 (0.6)
Asthenia	4 (1.2)	7 (2.0)

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Immune-mediated AEs

Event, n (%)	Durvalumab + GemCis (n=338)		Placebo + GemCis (n=342)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any immune-mediated AE*	43 (12.7)	8 (2.4)	16 (4.7)	5 (1.5)
Hypothyroid events	20 (5.9)	0	5 (1.5)	0
Dermatitis/rash	12 (3.6)	3 (0.9)	1 (0.3)	0
Pneumonitis	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.3)
Hepatic events	4 (1.2)	2 (0.6)	2 (0.6)	1 (0.3)
Adrenal insufficiency	4 (1.2)	0	1 (0.3)	0
Diarrhea/colitis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Hyperthyroid events	2 (0.6)	0	0	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	0	0
Pancreatic events	1 (0.3)	0	2 (0.6)	1 (0.3)
Hypophysitis	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Renal events	0	0	2 (0.6)	0
Myositis	0	0	1 (0.3)	1 (0.3)
Other rare/miscellaneous†	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

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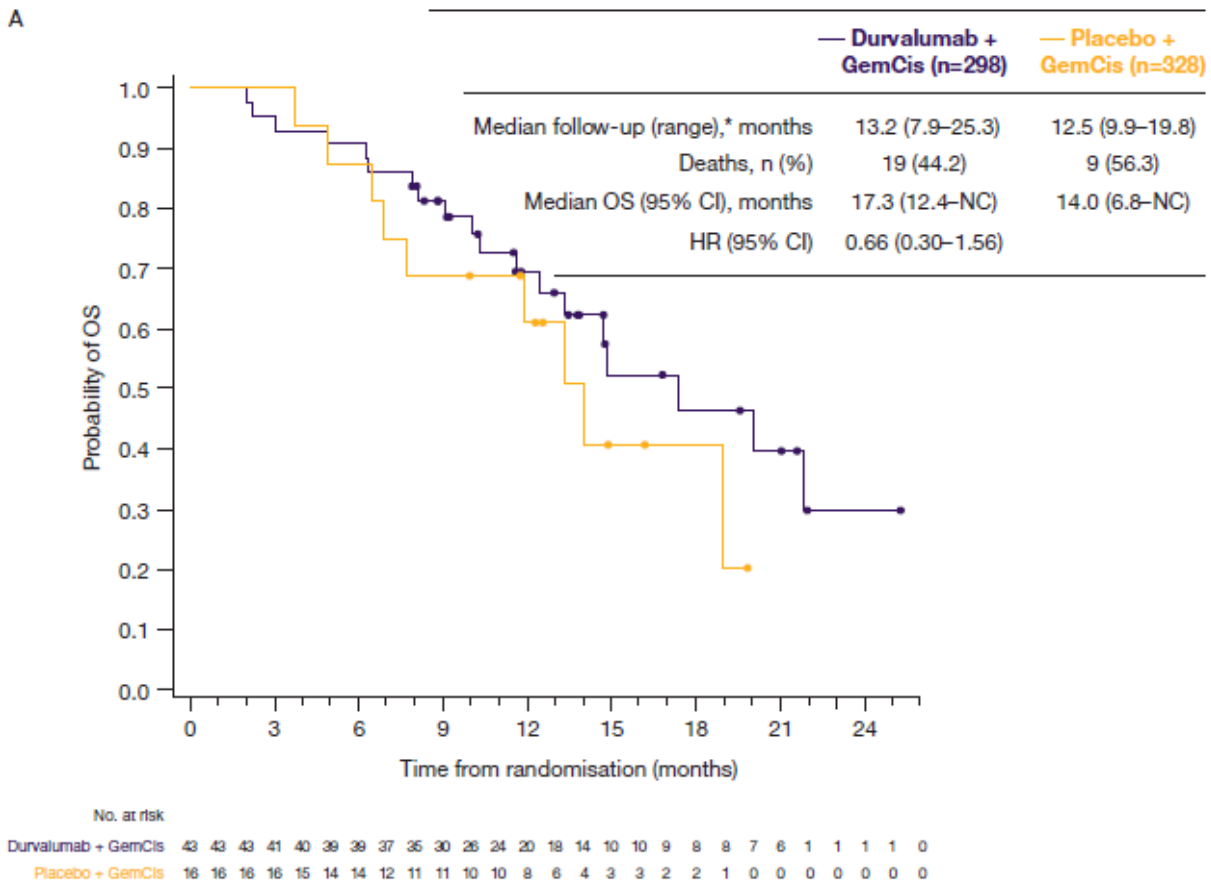
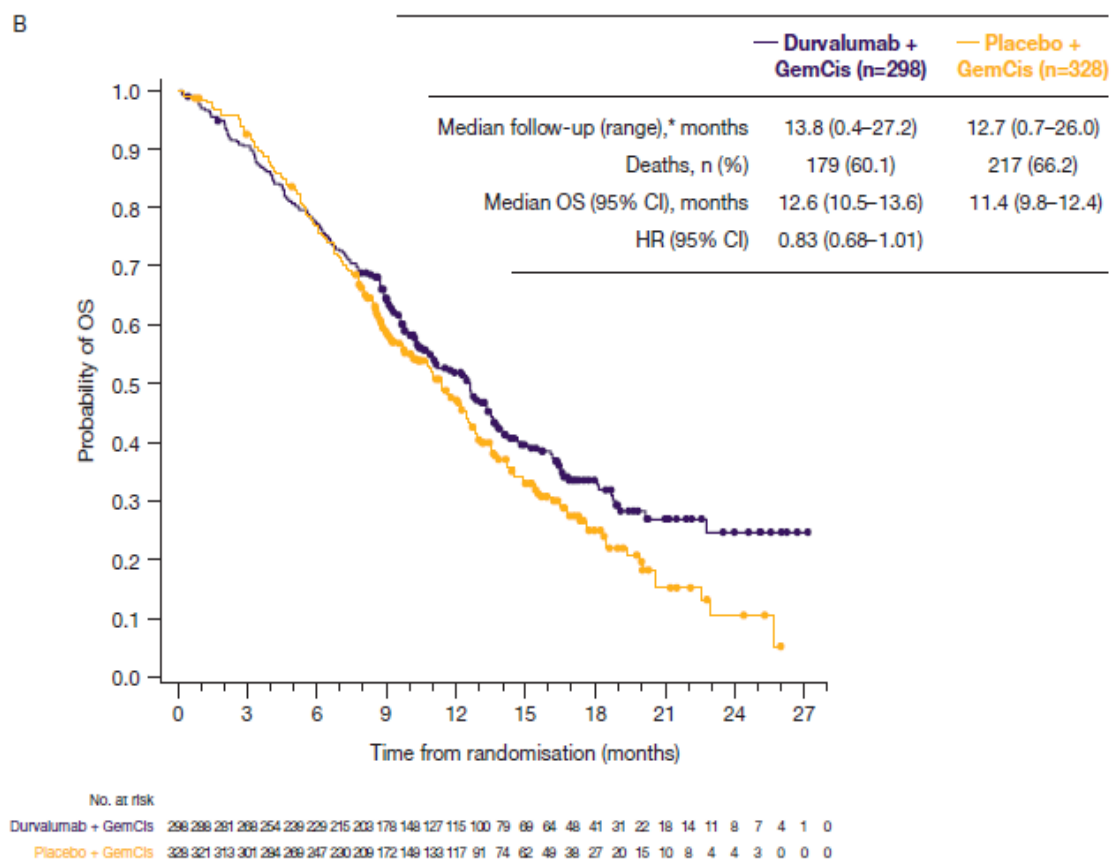
Immune-mediated AEs

- imAEs: association with OS

imAE (+) patients



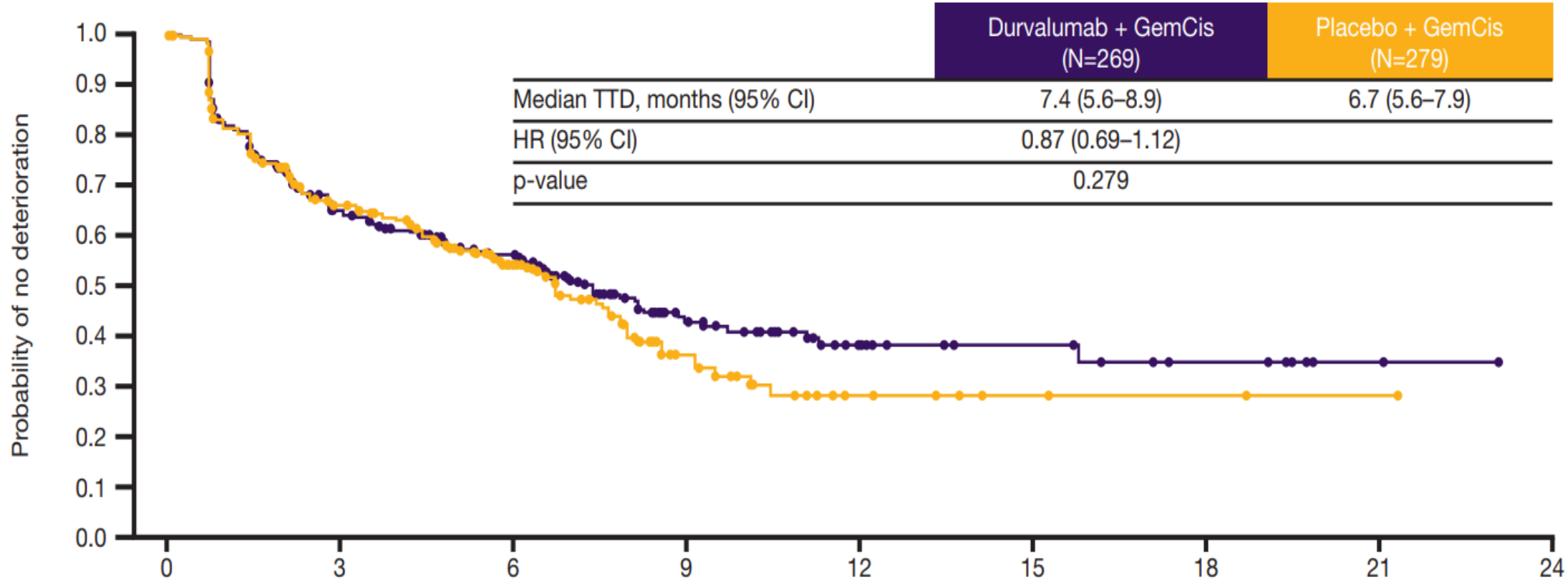
imAE (-) patients



Lorenzo A, et al. ESMO 2022

Patient-reported outcomes

- TTD of EORTC QLQ-C30 GHS/QoL



	Durvalumab + GemCis (N=269)	Placebo + GemCis (N=279)
Median TTD, months (95% CI)	7.4 (5.6–8.9)	6.7 (5.6–7.9)
HR (95% CI)	0.87 (0.69–1.12)	
p-value	0.279	

Number at risk

Durvalumab + GemCis	269	149	112	49	20	13	8	2	0
Placebo + GemCis	279	152	81	25	7	3	2	1	0

Burris, et al. ASCO 2022

NCCN Guideline Version 2.2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Biliary Tract Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,5]

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin (category 2B)
- Capecitabine + cisplatin (category 2B)
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* fusion-positive tumors:
  - Pralsetinib (category 2B)[12]

d Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy

5. Oh DY, He AR, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022:1-11. Epub ahead of print.

Durvalumab/ Gem-Cis regimen receives score 4 in ESMO-MCBS

Final Score (after adjustments)

Preliminary non-curative score	4
Final non-curative Score	4
Comment	EMA (CHMP) November 2022 pending EC decision FDA approval September 2022 for adult patients with locally advanced or metastatic biliary tract cancer
Issue date	22.09.2022
Release date	22.09.2022
Last update	14.11.2022

Indication details

Tumour Type	Gastrointestinal Cancers
Tumour Sub-type	Biliary tract cancer
Tumour stage	Unresectable or metastatic
Combined Agent(s)	Gemcitabine and cisplatin
Control Arm	Placebo + gemcitabine and cisplatin
Treatment Setting	In combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).
Trial Name	TOPAZ-1

Thank You